Claims

1. A method for generating a network of direct and indirect interaction partners of a disease-related (poly)peptide comprising the steps of

   (a) contacting a selection of (poly)peptides suspected to contain one or several of said direct or indirect interaction partners with said disease-related (poly)peptides and optionally with known direct or indirect interaction partners of said disease-related (poly)peptide under conditions that allow the interaction between interaction partners to occur;

   (b) detecting (poly)peptides that interact with said disease-related (poly)peptide or with said known direct or indirect interaction partners of said disease-related (poly)peptide;

   (c) contacting (poly)peptides detected in step (b) with a selection of (poly)peptides suspected to contain one or several (poly)peptides interacting with said (poly)peptides detected in step (b) under conditions that allow the interaction between interaction partners to occur;

   (d) detecting proteins that interact with said (poly)peptides detected in step (b);

   (e) contacting said disease-related (poly)peptide and optionally said known direct or indirect interaction partners of said disease-related (poly)peptide, said (poly)peptides detected in steps (b) and (d) and a selection of proteins suspected to contain one or several (poly)peptides interacting with any of the afore mentioned (poly)peptides under conditions that allow the interaction between interaction partners to occur;

   (f) detecting (poly)peptides that interact with said disease-related (poly)peptide and optionally said known direct or indirect interaction partners of said disease-related (poly)peptide or with said (poly)peptides identified in step (b) or (d); and

   (g) generating a (poly)peptide-(poly)peptide interaction network of said disease-related (poly)peptide and optionally said known direct or indirect interaction partners of said disease-related (poly)peptide and said (poly)peptides identified in steps (b), (d) and (f).

2. The method of claim 1, wherein said contacting step (e) is effected in an interaction mating two hybrid approach.

3. The method of claim 1 or 2, said method comprising after step (d) and before step (e) the steps of:

(d') contacting (poly)peptides detected in step (d) with a selection of (poly)peptides suspected to contain one or several (poly)peptides interacting with said (poly)peptides detected in step (d) under conditions that allow the interaction between interaction partners to occur; and

(d'') detecting proteins that interact with said (poly)peptides detected in step (d').

4. The method of any one of claims 1 to 3, wherein said disease-related protein is a protein suspected of being a causative agent of a hereditary disease.

5. The method of any one of claims 1 to 4, wherein said disease-related protein is huntingtin and wherein said interaction partners are the interaction partners as shown in tables 6, 7 or 9.

6. The method of any one of claims 1 to 5, said method comprising the step of determining the nucleotide sequence of a nucleic acid molecule encoding a direct or indirect interaction partner of the disease related protein.

7. The method of any one of claims 1 to 6, wherein said selections of proteins are translated from a nucleic acid library.

8. The method of any one of claims 1 to 7, wherein said selection of proteins in step (a) and/or (c) and/or (d') and/or (e) is the same selection or a selection from the same source.

9. The method of any one of claims 1 to 7, wherein said selection of proteins in step (a) and/or (c) and/or (d') and/or (e) is a different selection or a selection from a different source.

10. The method of any one of claims 1 to 9, wherein said method is performed by contacting the proteins on an array.

11. The method of any one of claims 1 to 10, wherein said interactions are detected by using the yeast two-hybrid system.

12. The method of any one of claims 1 to 11, containing after step (b), (d), (d") or (f) the additional steps of isolating a nucleic acid molecule with homology to said cDNA expressing the encoded protein and testing it for its activity as a modulator of huntingtin, wherein said nucleic acid molecule is DNA, or RNA, preferably cDNA, or genomic or synthetic DNA or mRNA.

13. A nucleic acid molecule encoding a modulator of huntingtin, wherein said modulator is a protein selected from table 8.

14. The nucleic acid molecule of claim 13, wherein said nucleic acid molecule is DNA, preferably cDNA, genomic DNA, or synthetic DNA or RNA, preferably mRNA.

15. The nucleic acid molecule of claim 13 or 14 fused to a heterologous nucleic acid molecule.

16. The nucleic acid molecule of claim 15, wherein the heterologous nucleic acid molecule encodes a heterologous (poly)peptide.

17. A vector comprising the nucleic acid molecule of any one of claims 13 to 16.

18. A host cell containing the nucleic acid molecule of any one of claims 13 to 16 or the vector of claim 17.

19. A method of producing a (poly)peptide, comprising culturing the host cell of claim 18 under conditions such that the (poly)peptide encoded by said polynucleotide is expressed and recovering said (poly)peptide.

20. A (poly)peptide comprising an amino acid sequence encoded by a nucleic acid molecule of any one of claims 13 to 16, or which is chemically synthesized, or is obtainable from the host cell of claim 18, or which is obtainable by the method of

claim 19 or which is obtainable from an in vitro translation system by expressing the nucleic acid molecule of any one of claims 13 to 16 or the vector of claim 17.

21. The (poly)peptide of claim 20 fused to a heterologous (poly)peptide.

22. A protein complex comprising at least two proteins, wherein said at least two proteins are selected from the group of interaction partners listed in table 9.

23. An antibody specifically recognizing the (poly)peptide of claim 20 or 21 or specifically reacting with the protein complex of claim 22.

24. The antibody of claim 23 which is polyclonal, monoclonal, chimeric, single chain, single chain Fv, human antibody, humanized antibody, or Fab fragment.

25. A method of identifying whether a protein promotes huntingtin aggregation, comprising

(a) transfecting a first cell with a nucleic acid molecule encoding a variant of the huntingtin protein or a fragment thereof capable of forming huntingtin aggregates;

(b) co-transfecting a second cell with

(i.) a nucleic acid molecule encoding a variant of the huntingtin protein or a fragment thereof capable of forming huntingtin aggregates; and

(ii.) a nucleic acid molecule encoding a candidate modulator protein identified by the methods of any one of claims 1 to 12 or a nucleic acid molecule encoding a modulator protein selected from table 6 or table 7;

(c) expressing the proteins encoded by the transfected nucleic acid molecule of (a) and (b);

(d) isolating insoluble aggregates of huntingtin from the transfected cell of (a) and (b); and

(e) determining the amount of insoluble huntingtin aggregates from the transfected cell of (a) and (b)

wherein an increased amount of huntingtin aggregates isolated from the transfected cells of (b) in comparison with the amount of huntingtin aggregates

isolated from the transfected cells of (a) is indicative of a protein's activity as an enhancer of huntingtin aggregation.

26. A method of identifying whether a protein inhibits huntingtin aggregation, comprising

(a) transfecting a first cell with a nucleic acid molecule encoding a variant of the huntingtin protein or a fragment thereof capable of forming huntingtin aggregates;

(b) co-transfecting a second cell with

(i.) a nucleic acid molecule encoding a variant of the huntingtin protein or a fragment thereof capable of forming huntingtin aggregates ; and

(ii.) a nucleic acid molecule encoding a candidate modulator protein identified by the methods of any one of claims 1 to 12 or a nucleic acid molecule encoding a modulator protein selected from table 6 or table 7;

(c) expressing the proteins encoded by the transfected nucleic acid molecule of (a) and (b);

(d) isolating insoluble aggregates of huntingtin from the transfected cell of (a) and (b); and

(e) determining the amount of insoluble huntingtin aggregates from the transfected cell of (a) and (b)

wherein a reduced amount of huntingtin aggregates isolated from the transfected cells of (b) in comparison with the amount of huntingtin aggregates isolated from the transfected cells of (a) is indicative of a protein's activity as an inhibitor of huntingtin aggregation.

27. The method of claim 25 or 26, wherein prior to step (d) the cells are treated with an ionic detergent.

28. The method of any one of claims 25 to 27, wherein the huntingtin aggregates are filtered or transferred onto a membrane.

29. A method for identifying compounds affecting an interaction of huntingtin or of a direct or indirect interaction partner of huntingtin comprising

(a) contacting interacting proteins selected from the group of interacting proteins listed in table 6 and/or table 7 in the presence or absence of an potential modular of interaction;

(b) identifying compounds capable of modulating said interaction.

30. The method of any one of claims 25 to 29 , further comprising

(a) modeling said compound by peptidomentics and

(b) chemically synthesizing the modeled compound.

31. The method of any one of claims 25 to 30, wherein said compound is further modified to achieve

(i) modified site of action, spectrum of activity, organ specificity, and/or

(ii) improved potency, and/or

(iii) decreased toxicity (improved therapeutic index), and/or

(iv) decreased side effects, and/or

(v) modified onset of therapeutic action, duration of effect, and/or

(vi) modified pharmakinetic parameters (resorption, distribution, metabolism and excretion), and/or

(vii) modified physico-chemical parameters (solubility, hygroscopicity, color, taste, odor, stability, state), and/or

(viii) improved general specificity, organ/tissue specificity, and/or

(ix) optimized application form and route

by

(i) esterification of carboxyl groups, or

(ii) esterification of hydroxyl groups with carbon acids, or

(iii) esterification of hydroxyl groups to, e.g. phosphates, pyrophosphates or sulfates or hemi succinates, or

(iv) formation of pharmaceutically acceptable salts, or

(v) formation of pharmaceutically acceptable complexes, or

(vi) synthesis of pharmacologically active polymers, or

(vii) introduction of hydrophilic moieties, or

(viii) introduction/exchange of substituents on aromates or side chains, change of substituent pattern, or

(ix) modification by introduction of isosteric or bioisosteric moieties, or

(x) synthesis of homologous compounds, or

(xi) introduction of branched side chains, or

(xii) conversion of alkyl substituents to cyclic analogues, or

(xiii) derivatisation of hydroxyl group to ketales, acetales, or

(xiv) N-acetylation to amides, phenylcarbamates, or

(xv) synthesis of Mannich bases, imines, or

(xvi) transformation of ketones or aldehydes to Schiff's bases, oximes, acetales, ketales, enolesters, oxazolidines, thiozolidines or combinations thereof.

32. A method of diagnosing Huntington's disease in a biological sample comprising the steps of

(a) contacting the sample with an antibody specific for a protein of table 6 or 7 or an antibody specific for the protein complex of claim 22; and

(b) detecting binding of the antibody to a protein complex,

wherein the detection of binding is indicative of Huntington's disease or of a predisposition to develop Huntington's disease.

33. The method of claim 32, wherein

(a) said protein complex contains GIT1 or

(b) said antibody is specific for a protein complex containing GIT1.

34. The method of claim 32, wherein

(a) said protein complex contains at least one protein selected from htt, HIP15 or HP28

(b) said antibody is specific for a protein complex containing at least one protein selected from htt, HIP15 or HP28.

35. A diagnostic agent/composition or pharmaceutical composition comprising the nucleic acid molecule of any one of claims 13 to 16, the (poly)peptide of claim 20 or 21 or the (poly)peptide mentioned in anyone of tables 6 and 7, the

antibody of claim 23 or 24, an antibody specifically reacting with a protein selected from table 7 and/or a protein selected from table 7.

36. Use of the molecule of any one of claims 13 to 16, the (poly)peptide of claim 20 or 21 or the (poly)peptide mentioned in anyone of tables 6 and 7, the antibody of claim 23 or 24, an antibody specifically reacting with a protein selected from table 7 and/or a protein selected from table 7, for the preparation of a pharmaceutical composition for the treatment of Huntington's disease.